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Nucleic Acid-based Cancer Therapy for Advanced-stage Solid Tumors: A Brief Overview

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Abstract

Introduction: The management of advanced-stage solid tumors remains a formidable challenge in oncology, often necessitating a combination of treatment modalities with limited efficacy. Nucleic acid-based drugs have emerged as promising therapeutic options, offering novel approaches to combat treatment-resistant tumors. This editorial review briefly analyzes viral and non-viral nucleic acid-based treatments for solid tumors, including their development, clinical activity, mechanisms of action, and prospects. Viral vectors, such as adenoviruses and lentiviruses, enable the delivery of therapeutic genes directly into tumor cells or the modulation of the tumor microenvironment, resulting in regulatory approvals for several gene therapies. Non-viral delivery systems, including lipid nanoparticles and polymer-based carriers, offer alternative strategies for transporting therapeutic nucleic acids into tumor cells, with precise drug release and targeting control.

Materials and Methods: The literature review is based on searches of the PubMed database, Web of Science, Scopus, and Google Scholar using specific keywords. The article is based on manuscripts published between 2021 and 2024.

Results: The mechanistic actions of nucleic acid-based drugs are diverse, encompassing direct tumor cell killing, modulation of the immune response, and inhibition of oncogenic pathways. Importantly, these therapeutic approaches demonstrate a favorable safety profile compared to traditional chemotherapy agents, minimizing off-target effects and reducing adverse events. The tumor microenvironment significantly influences the effectiveness of nucleic acid-based therapies, requiring strategies to improve drug delivery and overcome resistance mechanisms. Ongoing clinical trials, preclinical studies, and advancements in manufacturing and stability technologies are expected to drive the next generation of nucleic acid agents, ensuring widespread accessibility and clinical utility.

Conclusion: Nucleic acid-based drugs represent a transformative approach to cancer therapy, potentially revolutionizing treatment outcomes and ushering in an era of precision medicine in oncology.

Keywords: Antisense oligonucleotide, Nucleic acid-based drugs, Solid tumors, Tumor microenvironment, Viral/non-viral approach

1. Introduction

The treatment landscape for patients with advanced-stage solid tumors poses significant challenges, often requiring a multimodality approach involving surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Despite these efforts, many patients do not respond adequately to existing treatments, highlighting the urgent need for novel therapeutic strategies. Researchers have made significant strides in understanding the intricate architecture, biological functions, regulatory activity, and therapeutic potential of nucleic acids. Nucleic acid-based drugs have been approved by the U.S. Food and Drug Administration (FDA) and are available in the market [1]. Additionally, RNA interference (RNAi) and antisense oligonucleotide (ASO) are currently undergoing clinical trials. These and other nucleic acid-based drugs offer new hope for patients with otherwise refractory tumors [2]. They also show in combating solid tumors and genetic diseases. The clinical acceptance of this category of drugs is growing; however, challenges such as endosomal escape and extrahepatic targeting remain significant setbacks. Also, since it has to cross the lipid barrier of the plasma membrane, transfection using nude nucleic acids is not possible due to significant negative charges and large topographies. This problem has been mitigated by using some viral and non-viral delivery agents that provide favorable structures with remarkable transfection capacity. To achieve successful in vivo delivery and translational approach, it is important to protect nucleic acid-based drugs from nitration, oxidation, and nuclease digestion. Safe and effective delivery approaches can be discussed around viral and non-viral carriers [3]. The current molecular understanding may help achieve effective translation and the possibility of treating debilitating cancers. In this editorial, we delve into the development, clinical activity, mechanisms of action, and prospects of viral and non-viral nucleic acid-based treatments for solid tumors.

2. Materials and Methods

The literature review is based on searches of electronic databases, including PubMed, Web of Science, Scopus, and Google Scholar, using the keywords such as nucleic acid-based drugs, nucleic acid-based therapies, viral vectors + solid tumors, non-viral vectors + solid tumors, antisense oligonucleotide, and antisense RNAs. The article is based on manuscripts published between 2021 and 2024 in English. All duplicate articles were removed, and 19 manuscripts were finally selected for this brief review.

Development and clinical activity

Nucleic acid-based drugs encompass diverse therapies, including viral vectors (gene therapies) and nanoparticles containing mRNAs and other nucleotides. Viral vectors, such as adenoviruses and lentiviruses, have garnered attention for their ability to deliver therapeutic genes directly into tumor cells, either to induce cell death or to modulate the tumor microenvironment. Several viral-based therapies have received regulatory approval, marking a significant milestone in cancer treatment [4]. Non-viral approaches, including lipid nanoparticles and polymer-based carriers, offer alternative strategies for nucleic acid delivery [5]. These platforms facilitate the transportation of therapeutic nucleic acids, such as mRNAs encoding tumor-suppressive proteins or small interfering RNAs (siRNAs) targeting oncogenic pathways, into tumor cells. The versatility of non-viral delivery systems allows for precise control over drug release and targeting, minimizing off-target effects and enhancing therapeutic efficacy.

Mechanisms of action and tolerability

The mechanisms underlying the anti-tumor activity of nucleic acid-based drugs are multifaceted. Gene therapies aim to either directly kill tumor cells through the expression of cytotoxic genes or to modulate the immune response within the tumor microenvironment. mRNA-based therapies harness the cell's translational machinery to produce therapeutic proteins, while siRNAs and microRNAs (miRNAs) exert their effects by inhibiting the expression of specific target genes involved in tumorigenesis [6].

Major classes of these drugs include antisense oligonucleotides (ASOs), siRNAs, splice-switching oligonucleotides (SSOs), editing oligonucleotides (EONs), small activating RNAs (saRNAs), miRNA mimics, mRNA drugs [7], as summarized in Table 1.

ASO causes cleavage by RNase H in addition to producing a steric block via the creation of a robust double-stranded structure [8]. In the cytoplasm, a siRNA that has been absorbed by a cell forms a complex known as the RNA-induced silencing complex (RISC). Similar to ASOs, SSOs are a type of single-stranded DNA that regulates pre-mRNA splicing, producing mature mRNA. It is feasible to create double-stranded DNA and manipulate the splicing of particular exons by creating a sequence that is complementary to the exon-intron junction sequence of pre-mRNAs. Endogenous adenosine deaminase acting on RNAs (ADARs) recognizes artificially generated guide RNAs/EONs and uses them to initiate A-to-I RNA editing. Small activating

RNA (saRNA) are double-stranded RNAs that bind transcription factors to the target gene on genomic DNA and stimulate transcription from a target gene by recognizing an upstream region of the target gene. Given the similarities between saRNA molecules and siRNAs, it is anticipated that insights gained from siRNA modification will also apply to saRNAs. A synthetic double-stranded RNA called a miRNA mimic is created to replace a lost function in the body caused by a reduction in the expression of a miRNA (Figure. 1). This double-stranded RNA comprises a passenger strand that is either entirely or partially complementary to the guide strand, and a guide strand that is the same as the endogenous mature miRNA sequence. Without a vector system, the mRNA medications are injected straight into the target cells where they are produced as proteins. These medications differ from the class of oligonucleotide-based medications in that they are made up of hundreds to thousands of nucleotides [9].

Table 1. Therapeutic Nucleotides: Types, Functions, Structures, and Leading Companies

Name	Mode of action	Structure (with length)	Companies
siRNA	Inhibition	dsDNA (20-30 nt)	Alnylam, Quark, Dicerna
ASO	Inhibition	ssDNA (13-30 nt)	Nippon Shinyaku, Ionis
saRNA	Augmentation	dsDNA (20-30 nt)	MiNA
SSO	Splice switching	ssDNA (20-30 nt)	Ionis, Sarepta
miRNA mimic	Replacement	dsDNA (20-30 nt)	miReven, Mirna
mRNA	Replacement	ssDNA (hundreds – thousands nt)	Moderna, BioNTech
EON	Editing	ssRNA (20-40 nt)	ProQR

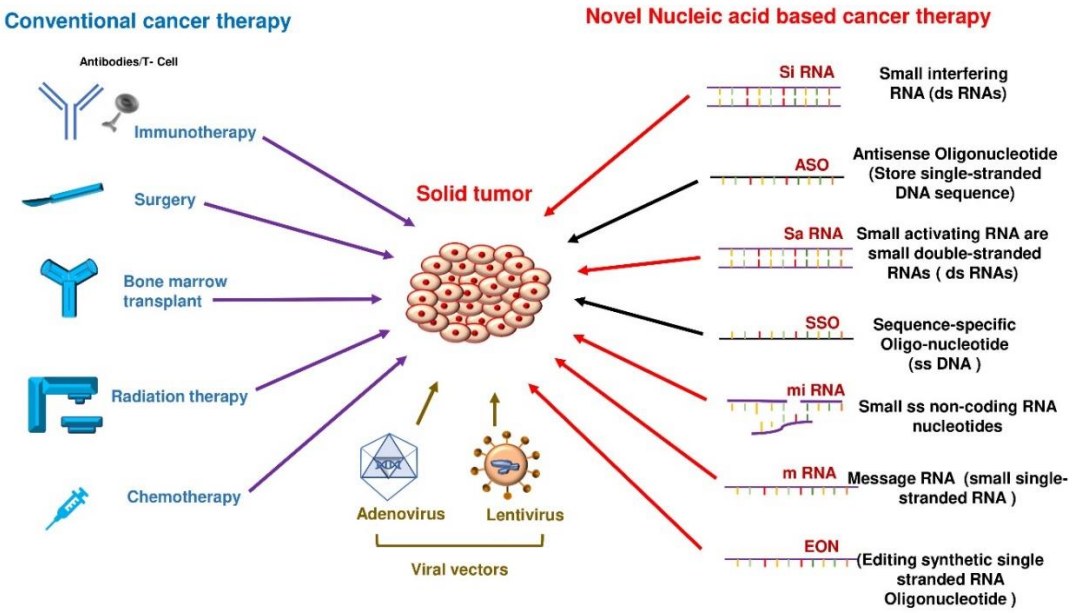

Figure. 1. Cancer treatment involving solid tumors requires conventional therapy (like surgery, chemotherapy, and radiation therapy, immunotherapy, and bone marrow transplant), which is usually not adequate and further requires an advanced and novel approach that involves nucleic acid-based drug therapy like mRNA. mRNA (messenger RNA) utilizes the cell's translational machinery to synthesize therapeutic proteins, miRNA and siRNA exert their effects by inhibiting the expression of tumor-specific genes, ASO (antisense oligonucleotides), a short single-stranded DNA, works by creating double-stranded steric block, SSO (sequence-specific oligonucleotides) are single-stranded DNA nucleotides that cause inactivation of specific DNA or RNA segments. SaRNA (Small activating RNA) are small double-stranded RNAs that bind transcription factors, target gene promoters and cause gene activation, EON (editing oligonucleotides) the small single-stranded RNA enables RNA editing. Another novel treatment approach is through viral vectors such as adenoviruses and lentiviruses, allowing the delivery of therapeutic genes directly into tumor cells

The most crucial factor in the clinical use of nucleic acid medications is getting the nucleic acids into the target tissues and cells. Since nucleic acids are very hydrophilic and polyvalent anionic, cells have a difficult time absorbing them. When given intravenously, they often end up accumulating in the kidneys and liver. Therefore, nucleic acid-based drugs without any drug delivery system are centered on targeting the liver and kidneys following systemic injection or on local delivery.

One of the key advantages of nucleic acid-based drugs is their favorable safety profile compared to traditional chemotherapeutic agents. By selectively targeting cancer-associated pathways, these therapies minimize damage to healthy tissues, thereby reducing the incidence of adverse effects commonly associated with conventional treatments. However, challenges remain in optimizing drug delivery and overcoming barriers imposed by the tumor microenvironment [10].

Nucleic acid-based drugs have limited biopharmaceutical properties, and their uses are limited in case of metastatic diseases. Their efficacy safety, tolerance, and activity depend on the choice of the delivery method and vehicle chosen. The delivery carriers may contribute to the localized retention of nucleic acids. Also, when given in combination, they may accumulate with other drugs, increasing the chances of adverse reactions.

Tumor microenvironment

The tumor microenvironment plays a critical role in shaping the efficacy of nucleic acid-based treatments. Factors such as hypoxia, extracellular matrix composition, and immune cell infiltration can influence the distribution and uptake of therapeutic agents within the tumor [11]. State-of-the-art research has revealed the decisive role of tumor microenvironment (TME) in treatment modalities, outcomes, and tumorigenesis as well. TME consists of a complex web of a variety of cell types, including endothelial cells (EC), immune (Th, Tc, antigen-presenting) cells, cancer stem cells (CSCs), cancer-associated fibroblasts (CAFs), cytokines, chemokines, several growth factors and the extracellular matrix (ECM). The TME cells interact with the cancerous cells and act through a variety of signaling mechanisms and pathways [12, 13]. This triggers tumorigenesis and defines the therapeutic responses. Hence, the interaction of nucleic acid-based drugs and TME appears as a potential area of research that can define the benefits and outcomes of such novel therapies [14]. Strategies to enhance drug delivery include the use of targeting ligands, modulation of the tumor vasculature, and combinational approaches to overcome resistance mechanisms.

Directions and considerations

Ongoing clinical trials and preclinical studies continue to unravel the potential of nucleic acid-based therapies in solid tumor management. Promising trends include the development of personalized treatments tailored to individual tumor profiles and the integration of nucleic acid drugs into existing treatment regimens [15, 16]. Additionally, advancements in manufacturing and stability technologies are poised to drive the next generation of nucleic acid agents, ensuring their widespread accessibility and clinical utility. To be effective, a nucleic acid-based drug should enter the body via a parenteral route and be able to cross the lipid membrane barrier of the cell and nucleus, unaltered, to be delivered to its target site for therapeutic action. Microneedling, apart from the above-mentioned vehicles, is an upcoming approach for nucleic acid-based drug delivery [17].

Although nucleic acid-based therapies have made staggering progress, advances in clinical chemistry and drug design have led to significant successful clinical applications, attracting researchers from academic and pharmaceutical groups [18]. Research and preclinical studies have focussed on improving the delivery of antisense oligonucleotide drugs; still, the evaluation of toxicity at every stage should not be neglected [19].

3. Conclusion

Nucleic acid-based drugs represent a paradigm shift in the treatment of advanced-stage solid tumors, offering novel therapeutic modalities with the potential to overcome treatment resistance and improve patient outcomes. With a deeper understanding of their mechanisms of action and the complex interplay within the tumor microenvironment, these innovative therapies hold promise for realizing the vision of precision oncology. As research advances, nucleic acid-based drugs are poised to revolutionize cancer therapy and usher in a new era of personalized medicine. Still, there exists a quest to understand a few queries. Firstly, most of the time, nucleic acid-based drugs are given in combinations. Therefore, the choice of vehicle, timings, and delivery site appears to define the efficacy of the formulations. The second one is identifying the bioavailability and activity of the carrier molecules toward the surrounding tissue environment. The final issue is addressing the population presenting with metastatic disease activity.

Ethical Considerations

Compliance with ethical guidelines

This article does not contain any studies involving human participants or animals performed by any of the authors. The submitted manuscript was approved by all co-authors

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Author's contributions

Mohd Mustafa and Badar ul Islam conceived and wrote the manuscript; Irfan Qadir Tantry and Safia Habib reviewed and edited the manuscript.

Conflict of interest

The authors declare that they have no discernible competing financial interests or personal connections that could be interpreted as influencing the conclusions made in this work.

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References

[1] Wang F, Li P, Chu HC, Lo PK. Nucleic Acids and Their Analogues for Biomedical Applications. Biosensors.2022;12(2):93. [DOI:10.3390/bios12020093]

[2] Huayamares SG, Loughrey D, Kim H, Dahlman JE, Sorscher EJ. Nucleic acid-based drugs for patients with solid tumours. Nature Reviews Clinical Oncology. 2024:1-21.[DOI: 10.1038/s41571-024-00883-1]

[3] de la Fuente IF, Sawant SS, Tolentino MQ, Corrigan PM, Rouge JL. Viral Mimicry as a Design Template for Nucleic Acid Nanocarriers. Front Chem. 2021;9:613209. [DOI:10.3389/fchem.2021.613209]

[4] Kaczmarek M, Poznańska J, Fechner F, Michalska N, Paszkowska S, Napierała A, Mackiewicz A. (2023). Cancer Vaccine Therapeutics: Limitations and Effectiveness-A Literature Review. Cells, 12(17), 2159. [DOI:10.3390/cells12172159]

[5] dos Santos Fonseca LM, Machado BA, Oliveira FO, de Jesus Santos JR, da Silva JW, Hodel KV, Rosatti BG, Pinto CD, Soares MB. An overview on recent patents and technologies on nanoparticles for nucleic acid delivery. Expert Opinion on Therapeutic Patents. 2024;34(3):171-86.. [DOI:10.1080/13543776.2024.2338097]

[6] Taibi T, Cheon S, Perna F, Vu LP. mRNA-based therapeutic strategies for cancer treatment. Molecular Therapy. 2024.[DOI: 10.1016/j.ymthe.2024.04.035]

[7] Yamada Y. Nucleic acid drugs—current status, issues, and expectations for exosomes. Cancers. 2021 Oct 5;13(19):5002. [DOI:10.3390/cancers13195002]

[8] Kaniowski D, Kulik K, Suwara J, Ebenryter-Olbińska K, Nawrot B. Boron Clusters as Enhancers of RNase H Activity in the Smart Strategy of Gene Silencing by Antisense Oligonucleotides. Int J Mol Sci. 2022;23(20):12190. [DOI:10.3390/ijms232012190]

[9] Wang P, Zhou Y, Richards AM. Effective tools for RNA-derived therapeutics: siRNA interference or miRNA mimicry. Theranostics. 2021;11(18):8771-96. [DOI: 10.7150/thno.62642] [PMID] [PMCID]

[10] Chen Y, Li Y, Li C, Zhang D, Liu Y, Zhang J, Guan S, Ding X, Xiao Q. The current perspective and opportunities of small nucleic acid-based therapeutics. Drug Development Research. 2024;85(2):e22164. [DOI: 10.1002/ddr.22164]

[11] Monaci S, Coppola F, Filippi I, Falsini A, Carraro F, Naldini A. Targeting hypoxia signaling pathways in angiogenesis. Frontiers in Physiology. 2024;15:1408750. [DOI: 10.3389/fphys.2024.1408750]

[12] Tang L, Mei Y, Shen Y, He S, Xiao Q, Yin Y, al. Nanoparticle-mediated targeted drug delivery to remodel tumor microenvironment for cancer therapy. International Journal of Nanomedicine. 2021:5811-29. [DOI:10.2147/IJN.S321416]

[13] Wessel KM, Kaplan RN. Targeting tumor microenvironment and metastasis in children with solid tumors. Curr Opin Pediatr. 2022;34(1):53-60. [DOI:10.1097/MOP.0000000000001082] [PMID] [PMCID]

[14] Neophytou CM, Panagi M, Stylianopoulos T, Papageorgis P. The Role of Tumor Microenvironment in Cancer Metastasis: Molecular Mechanisms and Therapeutic Opportunities. Cancers.2021;13(9):2053. [DOI:10.3390/cancers13092053]

[15] Eturi A, Bhasin A, Zarrabi KK, Tester WJ. Predictive and Prognostic Biomarkers and Tumor Antigens for Targeted Therapy in Urothelial Carcinoma. Molecules. 2024;29(8):1896. [DOI:10.3390/molecules29081896]

[16] Sheikhlary S, Lopez DH, Moghimi S, Sun B. Recent Findings on Therapeutic Cancer Vaccines: An

Updated Review. Biomolecules. 2024;14(4):503. [DOI:10.3390/biom14040503]

[17] Noh I, Lee K, Rhee YS. Microneedle systems for delivering nucleic acid drugs. J Pharm Investig. 2022;52(3):273-92. [DOI:10.1007/s40005-021-00558-4]

[18] Gubu A, Zhang X, Lu A, Zhang B, Ma Y, Zhang G. Nucleic acid amphiphiles: Synthesis, properties, and applications. Mol Ther Nucleic Acids. 2023;33:144-163. [DOI:10.1016/j.omtn.2023.05.022]

[19] Goyenvalle A, Jimenez-Mallebrera C, van Roon W, et al. Considerations in the Preclinical Assessment of the Safety of Antisense Oligonucleotides. Nucleic Acid Ther. 2023;33(1):1-16. [DOI:10.1089/nat.2022.0061]